Karolinska Institutet

**Institutionen för medicin**

# Vascular Progenitor Cells in Arterial Remodeling

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Rehabsalen, Norrbacka, S2:01, Karolinska Universitetssjukhuset.

**Fredagen den 8 april 2011, kl. 9.00**

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**Stockholm 2011**

## ABSTRACT

Cardiovascular disease is the leading cause of global mortality and physical disability mainly due to the complications such as myocardial infarction or stroke. Physiological healing reaction takes place in the diseased vessel wall aimed to repair the vessel after an injury. There are two factors essentially important for clinical improvement of vascular diseases. The first one is protection of the vascular damage, and the second one is repair of injured, ischemic and regenerating tissues to restore and maintain their function. The existing paradigm states that vascular progenitor cells are found in the vasculature and contribute to repair of injured blood vessel. However, the mechanism underlying the integration of these cells into the vasculature, their origin and specific functions has been unclear. This thesis presents a new understanding to this concept. Using human cardiac biopsies and animals models of arterial injury, we investigated whether progenitor cells can affect arterial repair and which mechanisms could be responsible for their action. Indeed, we have shown that adult vascular progenitor cells exist and possess a potential that extends beyond the cell types of their resident tissue. The vascular progenitor cells can be recruited either from bone marrow or blood vessel tissue in response to inflammation and migrate towards the sites of injury. Although, these cells are able to inhibit intimal hyperplasia, their contribution to formation of intimal lesion is not equal.

We provide evidence that inflammation and monocyte chemoattractant protein 1 (MCP-1) are pivotal in the recruitment of recipient-derived cells of smooth muscle cell phenotype into arterioles of transplanted human hearts. The number of these cells in the arterioles correlated strongly with the number of CD45-positive leukocytes and the grade of rejection, confirming that inflammation is strongly related to the recruitment of circulating progenitor cells into the graft vessels. This knowledge may be useful to design protocols for increase of progenitor cell numbers to limit tissue damage and facilitate healing at sites of tissue injury.

In our hands, bone marrow-derived cells, which are known source of stem cells and their progenitors, supported early stages of arterial injury and thereafter were eliminated from the artery wall. These cells localized in the arterial intima and the majority of them were of endothelial phenotype. Furthermore, bone marrow-derived cells were not able to fuse however could differentiate into vascular cells to adjust in the vessel wall and meet the demands and needs of their new microenvironment. Interestingly, local delivery of bone marrow-derived endothelial cells to the sites of arterial injury resulted in decrease of the intimal lesion area. Taken together, our results indicate the importance of these cells in the inhibition of early stages of intimal formation.

Further, we showed that enhanced inflammation in rat arterial allograft by acute infection with Cytomegalovirus (CMV) led to enhanced local MCP-1 production in the vasculature. Interestingly, CMV potentiated inflammation mainly in the adventitia, which resulted in migration of adventitial cells towards the intima and more rapid and severe intimal hyperplasia. Our findings increase understanding of the role of pathogens, such as CMV, in vascular remodeling and highlight that adventitial cells are able to migrate *in vivo* towards the sites of arterial injury, most likely in response to MCP-1.

We identified mesenchymal tissue-derived progenitor cells in vascular adventitia (Sca-1/CCR2, c-kit/CCR2) that contributed to vascular remodeling in a rat model of transplant vasculopathy. Early proliferation of cells in the adventitia coincided with an increase in the number of apoptotic cells in the media, and both proliferation and apoptosis were associated with inflammation. Inflammation and MCP-1 production were pivotal in the migration of mesenchymal progenitor cells derived from adventitia towards the intima.

In summary, this thesis presents novel evidence showing that inflammation and MCP-1 are important for recruitment of vascular progenitor cells to the sites of arterial injury and suggests tissue-derived mesenchymal progenitor cells, here derived from arterial adventitia, as a key source of cells for vascular repair. We believe that knowledge presented here not only increases understanding of vascular pathology but also provides unique value for understanding of unraveled aspects of tissue repair process.

ISBN 978-91-7457-256-8